Analog Computer in Drug Dosage and Formulation Design

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Methods have been described which utilize the analog computer as a laboratory aid in the preparation of drug formulations with improved therapeutic efficacy. Five basic dosage models were used to show the versatility of the computer and the variety of programs that are possible. These included single dosage, repetitive dosage, and three different types of sustained and delayed-release mechanisms. The analog computer may be used to predict which combination of existing formulas should be combined to give the desired response or may be used to provide specific information on the desirable physical characteristics of such formulas in advance of their manufacture. The major information needed for such predictions are the pharmacokinetic parameters specific to the drug in question. The analog computer provides an inexpensive means of predicting formulation requirements and may perform, in a matter of hours, work that might take weeks or months by normal laboratory screening methods.

IN AN ERA where both public opinion and federal legislation demand increased proof of drug efficacy and drug safety, the "art" of drug dosage and formulation design is being supplanted by the sophistications of advanced science and technology. Qualitative evaluations of drug potency and action are no longer adequate. Instead, the many transfer processes and reactions undergone by a drug during its release from the dosage forms and its passage through the body should be quantitatively described by mathematical models when reliable analytical data can be obtained. Models, originally formulated by Teorell (1), Dominguez (2), and others allow the description of a drug's action by listing certain numerical values obtained by mathematical treatment of experimental data. These values include rate constants for dissolution, absorption, tissue distribution, metabolism, and excretion. Such mathematical constants then become the focus of attention, an abstraction one level above the observed data (3). Also provided are quantifiable concepts that are extremely useful, such as metabolic half-lives and compartmental volumes of distribution which yield a pharmacokinetic profile or "fingerprint" for a drug. The work of Swintosky (4) on the drug sulfaethylthiadiazole is an excellent illustrative example. At best, however, the direct application of such analytical mathematical techniques is most approximate and difficult. The complexity of the mathematics involved leads to simplification of complex models and only sequential or parallel drug transferences are the models considered.

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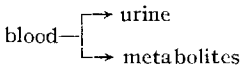
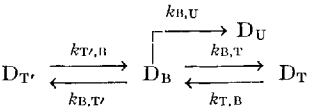
tablet → gastrointestinal tract →



DISCUSSION

The basic premises behind all such models include: (*a*) rapid equilibration of drug between blood and (*b*) other body tissues, fluids, or compartments.



The amount of drug in the blood (D_B) supposedly reflects and is proportional to the amount of drug in tissues T and T′ (D_T and $D_{T'}$) provided that the equilibration is extremely rapid. Furthermore, the rates of transfer must be invariant functions of the amounts of drug in each of these compartments (*i.e.*, first-order kinetics are followed). This implies that the compartmental sizes are limitless and the distribution model is independent of the magnitude of the dose. The slow rate-determining step must be either the elimination of the drug from the body or its metabolism, where these rates are proportional to the amount in the blood.

If both of these conditions are satisfied, then Eq. 1 will hold,

$$\log D_B = \frac{-k_e t}{2.303} + \text{constant} \qquad \text{(Eq. 1)}$$

and a plot of the logarithm of the blood concentration (D_B) *versus* time will result in a straight line with a slope of $-k_e/2.303$. In addition, the biological half-life, defined as that period of time needed for any blood concentration (after tissue equilibration is established) to reach one-half its value, will be constant for any blood level or dose chosen,

$$t_{0.5} = \frac{2.303 \log 2}{k_e} = \frac{0.693}{k_e} = \text{constant} \qquad \text{(Eq. 2)}$$

The k_e referred to here is the rate constant derived from the plotting of Eq. 1. It should be realized that this is not $k_{B,U}$ (the rate constant for urinary and/or metabolic elimination), but rather, is de-

pendent upon the ratios of other distribution rate constants (12).

$$k_e = \frac{k_{B,U}}{1 + \frac{k_{B,T}}{k_{T,B}} + \frac{k_{B,T'}}{k_{T',B}}} \quad \text{(Eq. 3)}$$

If the transfer of drug between one compartment, *e.g.*, T′, and the blood is an extremely slow process, for example, the slow release of thiopental from fatty tissues (5), or the deeper compartment for psicofuranine (13), this reaction then becomes rate determining and deviations from apparent first-order kinetics occur. A similar situation develops when a nonlinear Langmuir-type binding occurs, *e.g.*, the binding of sulfonamides to plasma proteins (6). When such phenomena occur, the "biological half-life" varies with the dose and loses its value as a descriptive entity since Eq. 2 no longer holds.

Another instance where the biological half-life concept may fall down is when one of the distribution compartments is of limited size. With increasing dose, the amount of drug stored in this compartment will increase until a saturation point is reached. At this point, nonlinear discontinuities will occur in the first-order kinetic distribution pattern.

These phenomena are difficultly described by available analytical mathematics. The advent of computers has provided a pharmaceutical research tool to handle such complex problems with efficiency and reliability.

The Analog Computer.—The analog computer is an extraordinary tool for the elucidation of the mechanisms and rates of transformations and distribution of drugs in *in vivo* and *in vitro* systems. It permits the determinations of models for absorption from the site of administration into the blood, diffusion into tissues, and other volumes of distribution (*i.e.*, lymph, cerebrospinal fluid, red blood cells, etc.), metabolic pathways, and excretion processes. Such determinations are carried out by programing the computer for any sequential, or parallel, changes in drug amount in the various depots of an organism. The "read-out" can be obtained as plotted curves of drug amount *versus* time for any selected compartment in the model chosen.

The theory and details of analog computer programing are presented in many excellent texts and brochures (7–12). In general, the analog computer can simulate postulated physiological models by a dynamic electrical network. Employing a set of linked integrators, the output from each integrator can represent the time-variable amount (drug concentration times the apparent volume of distribution) of the drug distributed in a particular biological compartment. The integrators are connected by rate setting potentiometers and summing amplifiers so as to simulate the distribution of the drug on the basis of the chosen model. Dosage is introduced by applying an initial condition voltage to either the "stomach" integrator or the "blood" integrator depending on whether oral or intravenous modes of administration are to be simulated.

Typical examples of such analog computer applications are found in the literature for the distribution of the nucleoside antibiotic psicofuranine (13) and for ^{47}Ca dynamics in the dog (14, 15). An elementary handbook for the practical application of analog computer methods to pharmacokinetics has also been presented (16).

Dosage Form Design.—A dosage form for oral administration has several prerequisites. (*a*) The dosage form (a tablet or a capsule) must disintegrate in the gastrointestinal tract and the powders or granules released must dissolve in the surrounding fluids. (*b*) The drug in solution must be absorbed by the gastrointestinal mucosa and be transferred into the blood. (*c*) If the blood level of the drug is proportional to its therapeutic response, the blood level achieved should be within the therapeutic concentration range for the desired duration of action. With many pharmacological agents, it is not necessarily true that blood levels directly reflect pharmacological activity. However, these discussions will be restricted to those cases where this is so. Blood levels in the subthreshold therapeutic range will result in ineffective biological activity, whereas concentrations above those eliciting the optimum response may yield toxic manifestations. For these reasons, drugs with a high therapeutic ratio (LD_{50}/ED_{50}) are normally used. (*d*) The duration of the therapeutic blood level should be optimum for the desired therapy. (*e*) The pharmacokinetic parameters which describe the absorption, distribution, metabolism, and excretion of the drug in the human should be known. They can be determined by definitely programed acute studies on intravenous and oral administration by methods which have been previously cited in the literature (13–15). This assumes that there is no change in the metabolic rate with continued administration as there is with barbiturates and many other drugs.

Theories of disintegration and dissolution have been covered in the recent pharmaceutical literature by Wagner (17), Higuchi (18), and others (19–21). Since this literature is both extensive and thorough, these theories will not be discussed herein.

The pH-partition theory of drug absorption through biological membranes has been discussed by Schanker in several review articles (22). The basic premises are that a drug will not be absorbed unless it is unionized and can be partitioned into a lipid-like membrane. These rules hold for drugs which are "passively" rather than "actively" transported in biological systems and permit estimates of ease of absorption. However, absorption rates can be quantified and used whether they are active or passive since, not withstanding the mechanism, they are largely concentration dependent.

Methods of prolonging blood levels, such as using enzyme poisons to slow drug metabolism or drugs to compete for excretory transport systems [*e.g.*, the use of probenecid to block the tubular secretion of penicillin (23)] have been used. These are objectionable both because of their lack of specificity of action and because of their tendency to alter the physiological *status quo*.

The study of the relationship between the physical and chemical properties of drugs and their administered dosage forms and the resultant biological effects has been called biopharmaceutics. The proper use of pharmacokinetic and biopharmaceutical techniques should achieve optimal therapeutic response from a given dose of drug.

Means by which such goals may be obtained are by systematic variation of the following factors: (*a*) the form of the drug (*i.e.*, free acid or base, ester, salt, complex, etc.); (*b*) the physical state (crystal or powder), particle size, and surface area; (*c*) the

presence or absence of other materials with the drug in the dosage form; (*d*) the type of dosage form in which the drug is administered; (*e*) the processes encountered during the manufacture of the dosage form. These alterations usually affect the absorption rate of the compound by controlling its rate of dissolution from the dosage form and into the gastrointestinal fluids. Since these methods alter only the time availability of the drug and not the biological system, they are obviously the methods of choice.

Application of Computer Techniques.—The purpose of this paper is to show how the analog computer may be programed to give information on how to improve the therapeutic efficiency of a drug formulation. Such information may be obtained in two ways. First, having a knowledge of the pharmacokinetics of the drug the proper dose and dissolution rate constants which will give optimum therapy may be ascertained. Second, using knowledge of the physical characteristics of available formulations, which combinations will provide the desired effect can be predicted.

With either or both of these methods, information can be provided faster, more accurately, and at lower cost than by the sole use of the *in vivo* and *in vitro* testing available. It must be stressed, however, that the ultimate test of therapeutic efficacy of drug formulations is in biological systems.

RESULTS AND DISCUSSION

The basic model used in these present computer studies on optimization of drug dosage forms was

$$GI \xrightarrow{k_{GI,B}} B \xrightarrow{k_{B,U}} U \qquad \text{(Eq. 4)}$$

where GI is the gastrointestinal compartment; B, the body compartment; U, the sum of excretory compartments (urine, metabolism, feces, etc.); $k_{GI,B}$ is the first-order rate constant for absorption of drug from the gastrointestinal tract into the blood; and $k_{B,U}$ is the sum of the first-order rate constants for loss (*i.e.*, glomerular filtration, metabolism, etc.) of the free, therapeutically active drug moiety from the body compartment.

This model was chosen for its simplicity since drug formulation rather than complex pharmacokinetics was being investigated. It should be remembered, however, that the computer can be used for any model where the kinetic patterns have been established. Indeed it may be only with the use of a computer that such complex models can be verified in the first place (13–15).

The assumptions that are inherent in the choice of this simple model are that (*a*) the sequential transfers from GI → B → U are by first-order processes and are therefore dependent on the drug amount in each compartment; (*b*) the drug used is nonionic in character and shows no variation in absorption due to pH changes along the length of the gastrointestinal tract; (*c*) the drug is completely absorbed; and (*d*) instantaneous equilibration of the drug occurs between all tissues permeable to the drug and the blood. At any time, therefore, the blood concentration of drug mirrors the concentrations in all drug-containing tissues.

The rate constants for absorption and elimination were held constant throughout the course of the experiment and had the following values:

$$k_{GI,B} = 4.60 \text{ hr.}^{-1}$$

$$k_{B,U} = 1.15 \text{ hr.}^{-1}$$

These values closely approximate those which may be calculated for an oral dose of 400,000 units of potassium penicillin V from the data of Holland *et al.* (24). The high absorption rate constant permits all (100%) of the dose to be absorbed in 1.5 hr., while the elimination rate constant allows the drug a biologic half-life of 0.6 hr.

A computer plot of the gastrointestinal, body, and urinary amounts of drug (labeled D_{GI}, D_B, and D_U, respectively) as fractions of an initial 10 units of drug given in solution or as a rapidly dissolving tablet, with time, is given in Fig. 1.

Certain clinical parameters are needed for proper design of dosage forms. For a given dose the threshold level for this drugs' action is considered to be 2.5 units of the total dose in the blood compartment with a maximum effect noted at 3.5 units (the upper and lower dashed lines of Fig. 1 demonstrate these values). It is interesting to note that only 14% of the dosage was used in the therapeutic range, 21% was expended in D_B levels above 3.5, and 65% at subthreshold levels.

The differential equations and analog computer program which describe the basic model are found in the *Appendix* under *Model I* (Eqs. 1*a*–1*c* and Fig. 2).

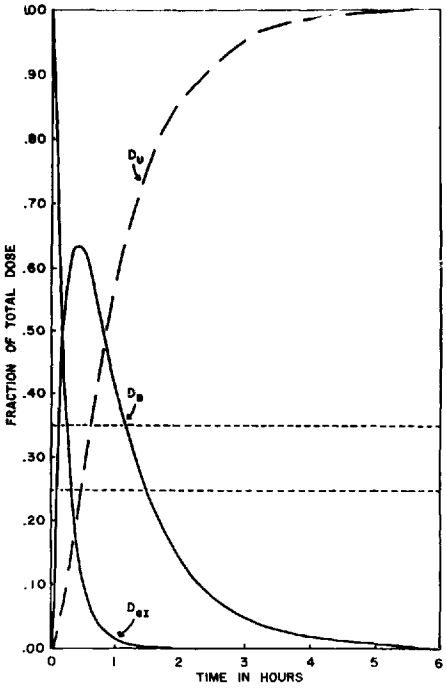


Fig. 1.—Analog computer plot of compartmental distribution of a single 10 unit dose of drug. D_{GI} = amount of drug in the gastrointestinal tract, D_B = amount of drug in the body, and D_U = amount of drug eliminated from the body. The interval between the dashed lines indicates the desired therapeutic range.

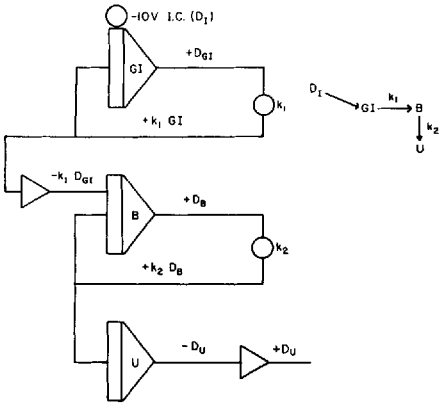


Fig. 2.—Analog computer program for a single 10-unit dose of drug administered in solution into the GI compartment (*Model I*).

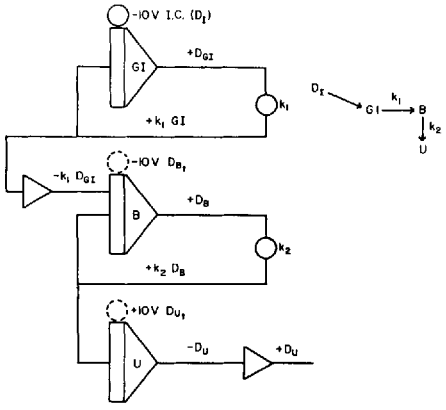


Fig. 4.—Analog computer program used for investigation of a multiple dosage regimen (5 units of drug every 1.2 hr.) (*Model II*).

A logical approach to maintain therapeutic levels with greater drug efficiency is multiple dose therapy. When a drug is administered on a multiple dose regimen with a constant dosage interval, the blood levels of the drug reach a steady state condition after several doses. This steady state is evidenced by the blood levels in a given dosage interval being essentially the same as those in the preceding and following intervals. For the authors' drug, the computer was dosed with half the original dose of Fig. 1 (5 units) at zero time followed by equal doses at consecutive 1.2 hr. intervals (2 half-lives) until 8.4 hr. The typical compartmental profile for such multiple dosing is seen in Fig. 3. The equations used for this approach are the same as those used for the basic model (*Model I*, Eqs. 1*a*–1*c*). The computer program involves only minor modifications of the one used for single dosing and is seen in *Model II* (*Appendix*) and Fig. 4. It is readily apparent that adjustments of dosage amounts and times are easily accomplished by slight modifications of the computer program to graphically evaluate optimum choices. In Fig. 3 therapeutic blood levels are maintained for the better part of 9 hr. The need for dosage form optimization is evident, however, to supplant the repetitive dosing regimen as well as to moderate the undesirable rising and falling of the body compartment levels.

Sustained and Delayed-Release Models.—The desirable qualities of oral sustained or delayed-release formulations have been listed by Rowland and Beckett (25) and include an initial and a maintenance dose to give and maintain blood concentrations of drug which elicit the desired therapeutic effects.

The benefits would be to reduce the frequency of drug administration compared with conventional dosage forms and to give a more uniform biological response with a reduced incidence and intensity of side effects.

In general, the total dose used in a sustained-release dosage form is the sum of the amount in the initially fast dissolving portion (D_I) and that present in the more slowly dissolving maintenance form

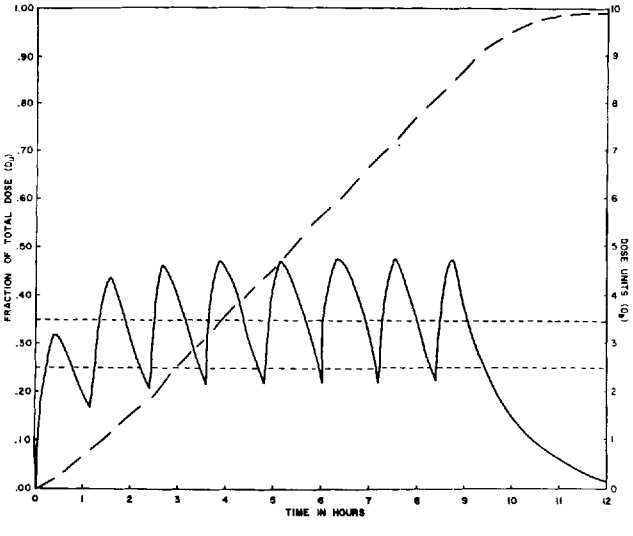


Fig. 3.—Compartmental levels of drug using a repetitive dosage regimen (5 units of drug every 1.2 hr.). The ordinates for blood level are given on the right in terms of units of drug. Key: – – – –, D_U; ———, D_B.

(D_M). As ideally postulated, the "loading" dose (D_I) will bring the drug amount in the body to its therapeutic level, while the D_M will maintain this level for the prescribed period of time.

The major prerequisite for the "loading" dose, D_I, is that it dissolve rapidly and completely. This end is normally achieved by either placing the drug in solution as an initial dose or formulating a conventional, fast disintegrating and dissolving tablet which, in essence, achieves the same goals. For the authors' purposes, D_I was placed on the computer as an initial condition on the GI compartment integrator (see *Appendix*). What this accomplishes is to have 100% of D_I in solution and ready for absorption at time zero.

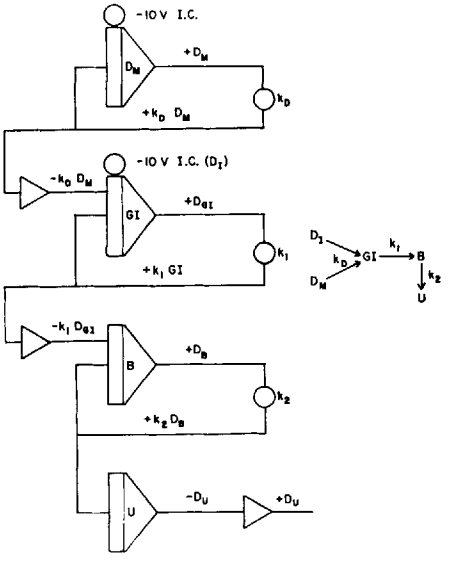


Fig. 5.—Analog computer program used for evaluation of first-order sustained-release dosage formulations (*Model III*).

The formulation and programing of the "maintenance" or slowly releasing form, D_M, is a problem of greater complexity. Three basic models for sustained and delayed-release formulations have been chosen.

First-Order Release.—Both Wiegand and Taylor (26) and Wagner (17) have shown that per cent released *in vitro versus* time data reported in the literature for the dissolution of many sustained-release preparations give linear pseudo (or apparent) first-order rates from about 0.5 hr. to the time the test was completed. Literature data subsequent to these papers have confirmed these observations and include: (*a*) drug embedded in an insoluble tablet matrix (27), (*b*) drug coated with waxy or polymeric materials (28), and (*c*) drug complexed with cation exchange resins (29). Since these preparations make up the predominant number of available sustained-release products, it was decided to investigate the programing of a first-order release rate for D_M as a method for prolonging the blood level of the drug under investigation.

The equations and program which describe this model are found in the *Appendix* under *Model III*, Eqs. 3*a*–3*d*, and Fig. 5.

An infinite number of first-order disappearances of D_M can be obtained by systematic alteration of the potentiometer corresponding to k_D (the rate constant for dissolution of D_M).

Using these k_D's and various combinations of D_I and D_M, the computer was then programed to determine the set of conditions which yield the maximum therapeutic benefit.

Figure 6 shows the type of sustained release obtained in a typical case with such a first-order loss from D_M. In this case, 10% of the total dose (which was twice the dose used in Fig. 3) is present as D_I, while 90% is D_M. The dissolution rate constant (k_D) for D_M was chosen as 0.375 hr.$^{-1}$.

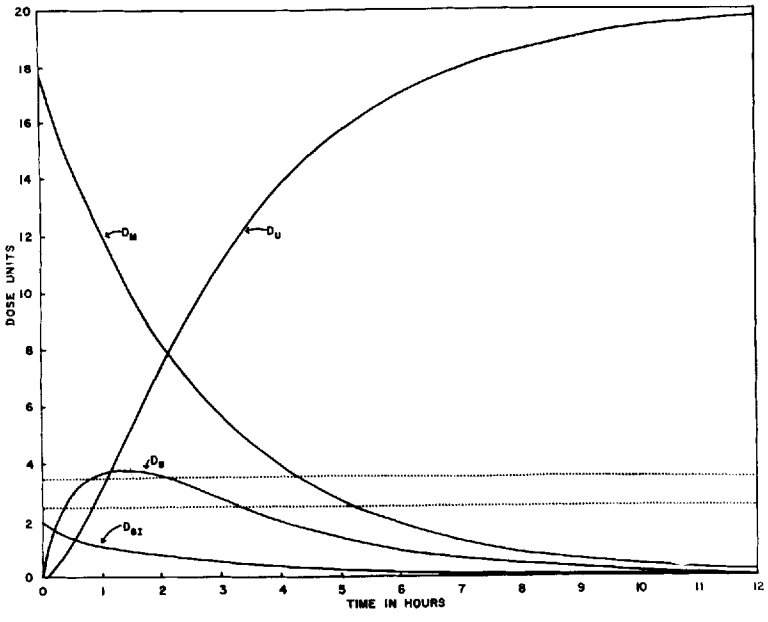


Fig. 6.—Effect of a first-order sustained-release maintenance dose (D_M) on compartmental drug levels. This formulation was programed to yield a drug-free system after 12 hr. D_I = 2 units; D_M = 18 units.

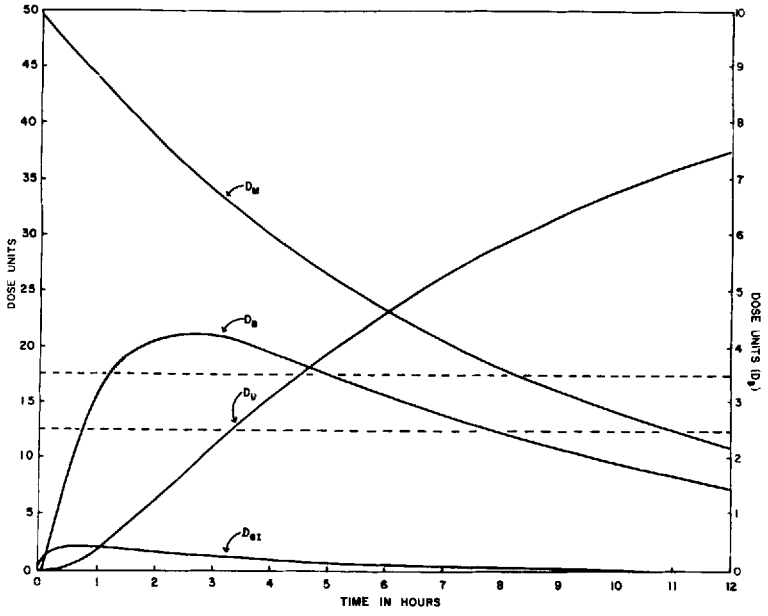


Fig. 7.—Effect of increasing amount of drug in D_M and decreasing k_D. No time limit was set here on the maintenance of drug in the body. The ordinates for blood level are given on the right. Key: D_M = 50 units; D_I = 0.

It would seem, at least for this drug, that a first-order mechanism for the release of the maintenance dose offers no significant improvement over multiple dosing. The optimum increase in blood level duration for twice the amount of drug is twice that obtained for the original dose. Other combinations of k_D, D_I, D_M lead to the same conclusions. When the dose or k_D is increased, drug levels in the body are increased. The only apparent advantage of such a sustained-release dosage design is the reduction in times of oral administration; there is no apparent increase in the efficient usage of the drug amounts. An illustration of this point is Fig. 7, where 5 times (50 units) the dose used in Fig. 1 is given with a k_D of 0.125 hr.$^{-1}$. The increased duration of blood level is only 5 times that observed for 10 units of drug.

Release from Coated Pellet Formulations.—Many companies now supply products in the form of a hard gelatin capsule containing round candy pellets upon which has been deposited a fixed amount of drug. Coated over the drug are one or more thicknesses of a waxy or polymeric coating, whose dissolution rate has been evaluated in both *in vitro* and *in vivo* systems.

When either the thickness or the type of coating substance is varied, it is possible to obtain several different populations of drug pellets. If the appearance of drug in solution is measured with time, the drug will only appear after the protective coating has been ruptured, dissolved, or digested away.

If the situation was ideal, and all members of a given population of pellets had exactly the same coating thickness, *i.e.*, the variance among pellets was zero, the drug in solution *versus* time plot should show a lag period (equal to that amount of time necessary to rupture, dissolve, or digest the protective coating) followed by a steep, almost instantaneous, appearance of all the drug from this population of pellets into solution. This would be a direct simulation of the repetitive dosage regimen we have previously considered in *Model II* and Fig. 3.

What is far more likely, however, is that a finite wide variance does indeed exist within a chosen population of pellets. This being the case, the dissolution of the population of pellets is not instantaneous, but rather normally distributed with mean $\bar{t}$ and variance, σ^2. Integration of the area under the normal curve, number of pellets ruptured, or releasing drug *versus* time, will give the amount of drug in solution. A plot of this integral *versus* time will yield a symmetrical sigmoid curve whose midpoint is $\bar{t}$.

In accordance with the authors' postulated model, the release of drug from the pellet types occurs at separated intervals with a Gaussian distribution of release about the mean of this interval. The amount of drug which is to be released at each interval is a function of the numbers of pellets so formulated. The release of drug from each pellet is relatively instantaneous; the release of total drug for that pellet type is normally distributed about the mean time of release of that pellet population. If a dosage form is produced with 100 or more populations of effective thicknesses with each containing equivalent total amounts of drug an over-all zero-order release can be simulated.

Figure 8 demonstrates a typical compartmental profile using a pellet-type formulation; the D_I = 5 dose units and the D_M consisted of 4 populations of pellets (each containing 5 units of drug) with different mean times of release. The standard deviation about these mean times of release was considered to be the same for each population in this case. The D_B and D_{GI} are plotted in terms of dose units in the respective compartment while D_U is shown on scale as 0.4 times the actual dosage units excreted.

Several studies in the literature (30–32) have demonstrated a simulation of t.i.d. dosing with coated pellet sustained release. Per cent release data for 5 bulk pellet groups, presented in one paper (30), support the normal distribution postulate.

The rather unique equations and programs used to simulate the normally distributed pellet popula-

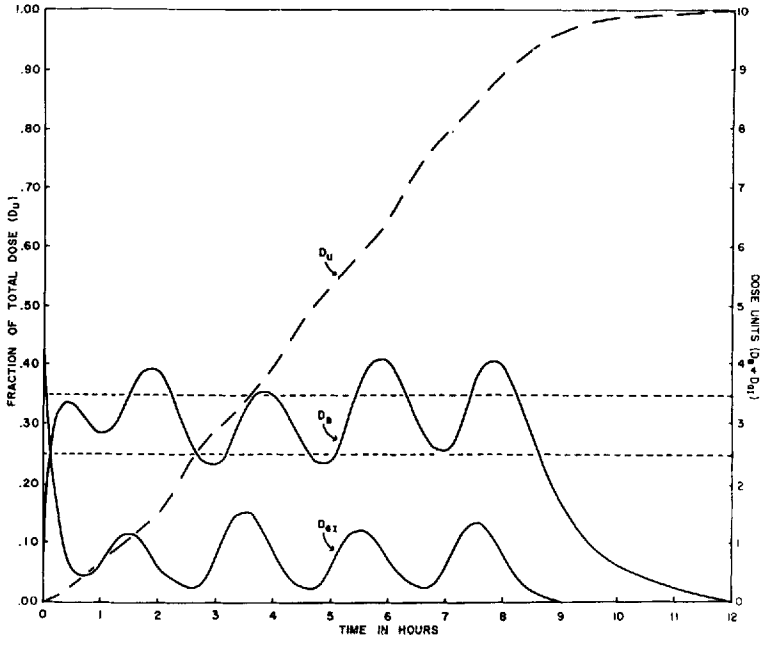


Fig. 8.—A simulated repetitive dosing compartmental profile obtained after a single dose of a coated pellet formulation. Four pellet populations, each containing 5 units of drug, with the same standard deviation but different mean times of dissolution were used in addition to 5 units of immediately dissolving D_I.

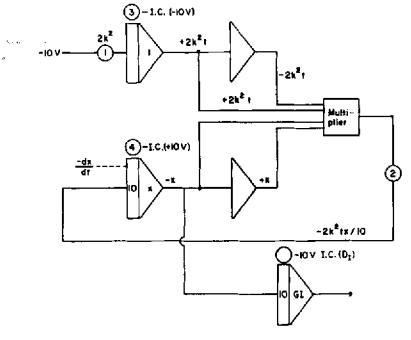


Fig. 9.—Analog computer program for the generation and integration of a Gaussian type distribution (coated pellet type of sustained release). The remainder of the program is the same as in Fig. 2 (*Model IV*).

tions (33) are found in the *Appendix* under *Model IV*, Eqs. 9–12, and Fig. 9, respectively.

Zero-Order Release.—The ideal mechanism to maintain a constant blood level is to release drug from D_M by zero-order kinetics (*i.e.*, at a constant rate independent of concentration).

To achieve optimum therapy, the rate of change of drug in the blood (D_B) with time should be zero. Since this rate is the difference between the rate of absorption and the rate of excretion

$$dD_B/dt = k_{GI,B}D_{GI} - k_{B,U}D_B = 0 \quad \text{(Eq. 5)}$$

it follows that the amount of drug in the gastrointestinal tract, D_{GI}, should be a constant for a desired blood level, D_B, since from Eq. 5,

$$D_{GI} = \frac{k_{B,U}}{k_{GI,B}} D_B \quad \text{(Eq. 6)}$$

It also follows that the amount of drug in the gastrointestinal tract, D_{GI}, should remain invariant with time

$$dD_{GI}/dt = dD_M/dt - k_{GI,B}D_{GI} = 0 \quad \text{(Eq. 7)}$$

From Eqs. 6 and 7 the rate of release from the maintenance dose should be

$$\frac{dD_M}{dt} = \frac{k_{B,U}}{k_{GI,B}} \cdot k_{GI,B}D_B = k_{B,U}D_B \quad \text{(Eq. 8)}$$

Thus, the rate of release from the maintenance dose D_M must be constant and equal to the rate of loss of drug from the blood at a blood level corresponding to D_B. This rate is given by Eq. 8.

Zero-order release may be feasible in *in vivo* situations when the drug has a limited solubility in the gastrointestinal fluids. Under the circumstances, the drug will initially dissolve at a rate proportional to the amount of drug remaining in the tablet until a saturated solution is formed in the gastrointestinal fluids. Afterward, the drug should dissolve at the same rate as it is absorbed with a net result of a constant dissolution rate.

Figure 10 demonstrates the compartmental profile for a formulation containing $D_I = 4$ units and $D_M = 6$ units (solid line) and $D_I = 4$ units, $D_M = 16$ units (dashed line). The solubility (D_S) was chosen at 4.0 drug units. The improvement in therapeutic effect over those conditions used in Fig. 1 can be observed here where the desired blood level has a duration of 1.9 hr. compared to the 1.4 hr. noted with a conventional dosage form.

The equations used to predict the k_D required for the D_M of Fig. 10 as well as those describing the model are found under *Model V* (*Appendix*). The computer program for zero-order release is Fig. 11.

APPENDIX

Model I.—*Computer Simulation of a Single, Rapidly Dissolving Dose.*—A single dose, in solution

$$D \longrightarrow GI \xrightarrow{k_{GI,B}} B \xrightarrow{k_{B,U}} U$$

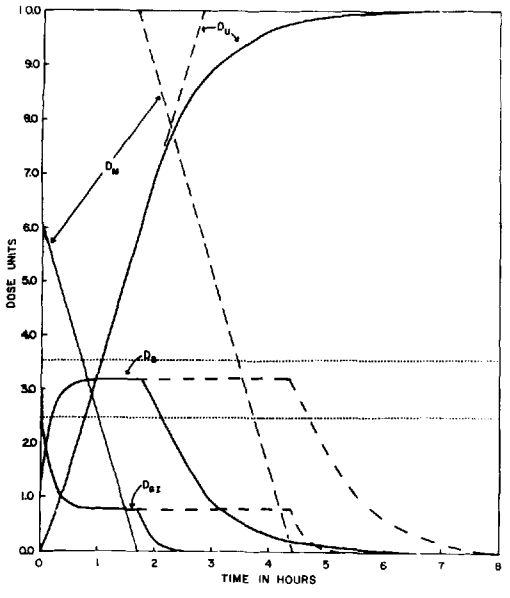


Fig. 10.—Effect of a zero-order sustained-release dosage form on compartmental drug levels. The solid lines are for a formulation containing $D_I = 4$ units and $D_M = 6$ units, while the dashed lines are for $D_I = 4$ units and $D_M = 16$ units of drug.

in the GI compartment at time zero is absorbed into, and lost from, the blood at a rate proportional to the residual drug concentration.

$$-\frac{dD_{GI}}{dt} = k_{GI,B}D_{GI} \qquad \text{(Eq. 1}a\text{)}$$

$$-\frac{dD_B}{dt} = k_{B,U}D_B - k_{GI,B}D_{GI} \qquad \text{(Eq. 1}b\text{)}$$

$$\frac{dD_U}{dt} = k_{B,U}D_B \qquad \text{(Eq. 1}c\text{)}$$

The computer program resulting from these equations is seen in Fig. 2.

Model II.—*Computer Simulation of Repetitive Dosing Regimen.*—One-half of the dose used in

$$D \longrightarrow GI \xrightarrow{k_{GI,B}} B \xrightarrow{k_{B,U}} U$$

Model I is administered at time zero followed by the same dose every 2 half-lives (1.2 hr.). The equations describing repetitive dosing are identical to Eqs. 1*a*–1*c*. The computer program, Fig. 4, is essentially the same, differing only by the presence of initial condition potentiometers on the blood and urine integrators. At the beginning of each dosage interval the computer is stopped and these potentiometers are used to place the amount of drug remaining from the previous dosing in each compartment. For example, referring to Fig. 3, the amount of drug placed on the blood potentiometer at $t = 1.2$ hr. ($t = 0$ for dose 2) was 1.7 dose units.

Model III.—*Computer Simulation of First-Order Sustained Release.*—Dosage forms:

$$\begin{matrix} D_I \longrightarrow \\ D_M \overset{k_D}{\longrightarrow} \end{matrix} GI \xrightarrow{k_{GI,B}} B \xrightarrow{k_{B,U}} U$$

A combination of immediately soluble D_I and slowly releasing D_M is given at time zero. The rate of release of D_M is proportional to the amount of D_M remaining in the dosage form.

$$-\frac{dD_M}{dt} = k_D D_M \qquad \text{(Eq. 3}a\text{)}$$

$$-\frac{dD_{GI}}{dt} = k_{GI,B}D_{GI} - k_D D_M \qquad \text{(Eq. 3}b\text{)}$$

$$-\frac{dD_B}{dt} = k_{B,U}D_B - k_{GI,B}D_{GI} \qquad \text{(Eq. 3}c\text{)}$$

$$\frac{dD_U}{dt} = k_{B,U}D_B \qquad \text{(Eq. 3}d\text{)}$$

The computer program used to predict the optimum D_M and k_D for sustained therapeutic blood levels is seen in Fig. 5.

Model IV.—*Computer Simulation of a Coated Pellet Type of Sustained Release.*—Several populations of pellets, whose dissolution pattern follows a normal distribution, are combined to yield, upon administration of a single dose, a compartmental profile similar to that obtained with repetitive dosing.

A unique method was found (33) for computer simulation of a normal distribution and is as follows.

The frequency distribution which describes the normal distribution (Gaussion errror function) is

$$f(\gamma) = \frac{1}{\sqrt{2\pi}\sigma} e^{-(\gamma-\mu)^2/2\sigma^2} \qquad \text{(Eq. 9)}$$

or

$$x = Ae^{-k^2t^2}$$

where

$$A = \frac{1}{\sqrt{2\pi}\sigma}, \; k = \frac{1}{\sqrt{2}\sigma}, \text{ and } t = \gamma - \mu \qquad \text{(Eq. 10)}$$

The first derivative of Eq. 10 is

$$\frac{dx}{dt} = -2Ak^2te^{-k^2t^2} \qquad \text{(Eq. 11)}$$

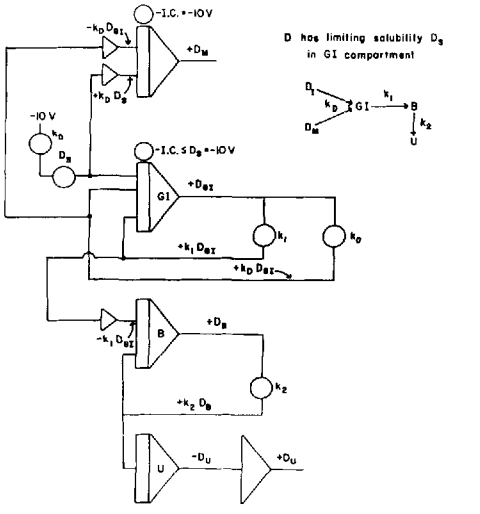


Fig. 11.—Analog computer program for evaluation of solubility limited, zero-order sustained-release dosage formulations (*Model V*).

Substituting Eq. 11 into Eq. 10 one obtains

$$\frac{dx}{dt} + 2k^2tx = 0 \qquad \text{(Eq. 12)}$$

The analog computer program for Eq. 12 is seen in Fig. 9. The plotted output of the x integrator gives the bell-shaped curve expected for the Gaussion error function. Integration of the area under this curve gives the amount of drug released into the gastrointestinal tract (D_{GI}). The remainder of the program (for D_{GI}, D_B, and D_U) is the same as in Fig. 2.

Model V.—*Computer Simulation of a Zero-Order Sustained-Release Mechanism.*—Let drug D have a

$$\begin{matrix} D_I \longrightarrow \\ D_M \text{---}\rfloor \end{matrix} GI \xrightarrow{k_{GI,B}} B \xrightarrow{k_{B,U}} U \qquad k_D$$

finite, limiting solubility (D_S) in the gastrointestinal tract. Let the initial dose, D_I, present as an initial condition in the GI compartment be equal to or less than D_S. As saturation is approached, the release of D_M will become constant.

The equations used for this program are

$$-\frac{dD_M}{dt} = k_D(D_S - D_{GI}) \qquad \text{(Eq. 4}a\text{)}$$

$$-\frac{dD_{GI}}{dt} = k_{GI,B}D_{GI} + k_DD_{GI} - k_DD_S \qquad \text{(Eq. 4}b\text{)}$$

$$-\frac{dD_B}{dt} = k_{B,U}D_B - k_{GI,B}D_{GI} \qquad \text{(Eq. 4}c\text{)}$$

$$\frac{dD_U}{dt} = k_{B,U}D_B \qquad \text{(Eq. 4}d\text{)}$$

The program corresponding to these equations is seen in Fig. 11.

The calculations used to predict the exact k_D required are as follows. Since Eq. 4*c*

$$-\frac{dD_B}{dt} = k_{B,U}D_B - k_{GI,B}D_{GI}$$

For a sustained blood level, $\frac{dD_B}{dt} = 0$, and the D_{GI} necessary is

$$D_{GI} = \frac{k_{B,U}}{k_{GI,B}} D_B \qquad \text{(Eq. 13)}$$

for D_{GI} to be constant, $dD_{GI}/dt = 0$ and, from Eq. 4*b*

$$k_{GI,B}D_{GI} = k_D(D_S - D_{GI}) \qquad \text{(Eq. 14)}$$

and, since D_S, D_{GI}, and $k_{GI,B}$ are known, the necessary k_D can be calculated

$$k_D = \frac{k_{GI,B} \cdot D_{GI}}{D_S - D_{GI}} \qquad \text{(Eq. 15)}$$

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